

# SUPPLEMENT

## **Savella (Milnacipran HCl): A New Option for the Management of Fibromyalgia**

### **Stakeholder Perspectives**

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# Savella (Milnacipran HCl): A New Option for the Management of Fibromyalgia

By Loretta Fala, Medical Writer

Fibromyalgia (FM) is a condition characterized by chronic, widespread soft-tissue pain with tender points along with other symptoms, often resulting in functional impairment. Affecting an estimated 2% to 4% of the US population, generally first diagnosed between the ages of 20 and 50 years, FM is about 7 times more common in women than in men.<sup>1</sup> The incidence of FM rises with age. By age 80 years, approximately 8% of adults meet the classification of FM set forth by the American College of Rheumatology (ACR).<sup>2</sup> Patients with lupus, rheumatoid arthritis (RA), or ankylosing spondylitis are at risk for FM.<sup>1</sup>

## Burden of Illness

FM is costly to the individual patient and to society. In the United States, costs attributed to FM are estimated at \$12 billion to \$14 billion annually and are associated with a loss of 1% to 2% of the nation's overall productivity.<sup>3</sup> According to a 2007 study, 34% of patients with FM spend between \$100 to \$1000 monthly above their insurance coverage to visit a clinician.<sup>3</sup>

The mean annual healthcare costs are approximately 3 times higher among patients with FM than those without FM.<sup>3</sup> Pain-related medication costs account for about 11% of the total costs.<sup>3</sup> In addition, twice as many patients with FM use nonpain medications, including antibiotics, cough and cold medications, and ulcer drugs.<sup>3</sup>

Employees with FM incur total annual costs nearly twice as high as other employees.<sup>4</sup> They also incur medical and drug costs that are a staggering 86% higher than costs incurred by others.<sup>4</sup> Moreover, based on a multicenter survey designed to assess the work and disability status of 1604 patients with FM, an estimated 26.5% of workers receive some form of disability payment.<sup>5</sup> For employees with FM, the prevalence of disability is estimated to be twice as high as that of all employees.<sup>2</sup>

Failure to diagnose a true case of FM is costly in terms of medical resources and can result in excess visits to a general practitioner, as well as excess prescriptions, referrals, and diagnostics.<sup>2,6</sup> Conversely, diagnosed cases of FM lead to savings and a decrease in resource utilization, particularly for tests and imaging studies.<sup>6</sup>

## Fibromyalgia Diagnosis

FM may be accompanied by many symptoms, including fatigue, sleep disturbances, morning stiffness,

cognitive difficulties, headaches and migraines, irritable bowel syndrome, mood disturbances, temporomandibular joint dysfunction, and environmental sensitivities.<sup>2,7,8</sup> Often diagnosed by primary care physicians, FM accounts for an estimated 15% to 20% of visits to rheumatologists, second only to osteoarthritis as the most common presenting factor.<sup>7,9</sup>

Although FM is not life threatening,<sup>10</sup> it can have a significant impact on a patient's quality of life (QoL) and daily functioning.<sup>11</sup> Based on a study comparing QoL of women with FM with that of women with RA, osteoarthritis, permanent ostomies, insulin-dependent diabetes, and healthy controls, women with FM consistently scored lowest in all categories.<sup>12</sup>

FM is recognized as a legitimate clinical entity by the American Medical Association, National Institutes of Health, World Health Organization, ACR, and the US Food and Drug Administration (FDA).<sup>11,13</sup> Recent studies suggest that patients with FM have a generalized disturbance in pain processing and an amplified response to stimuli.<sup>2</sup> Alterations occurring in the central nervous system (CNS) and at the periphery may contribute to the sensation of pain.<sup>14</sup>

The perception of pain involves a complex interaction between the ascending and descending pathways, with the ability to change the dynamic between stimulus and response.<sup>14</sup> Moreover, the descending pathway systems may have an important role in central sensitization.<sup>14</sup>

Neurotransmitter defects in ascending and descending CNS pathways contribute to the pain associated with FM.<sup>15,16</sup> The neurotransmitters serotonin and norepinephrine play a role in descending pain-inhibiting pathways.<sup>14,15</sup> Another neurotransmitter, substance P, is an 11 amino acid neuropeptide being studied for its presumed role in pain transmission.<sup>14</sup> Substance P coexists with glutamate in afferent terminals of the spinal cord.<sup>14</sup> Abnormalities associated with norepinephrine and serotonin have been seen in patients with FM.<sup>14,15</sup> Data suggest a potential decrease in serotonin- and norepinephrine-related activity in patients with FM.<sup>14</sup> Conversely, increased levels of substance P and glutamate have been seen in these patients.<sup>14,16</sup> Against this background, increasing attention is focused on the CNS and aberrant pain processing as the underlying mechanism of FM.<sup>2</sup>

Despite increasing recognition, FM continues to be overlooked and misdiagnosed, and its diagnosis is often

delayed.<sup>7,11</sup> Because its symptoms are similar to other disorders, FM is difficult to diagnose.<sup>7</sup> Conditions that must be ruled out before FM diagnosis include RA, polymyalgia rheumatica, hypothyroidism, and lupus.<sup>17,18</sup> If compelling evidence exists, other tests, such as a Lyme antibody, may be warranted.<sup>18</sup>

The diagnostic criteria for FM established by the ACR include a history of widespread pain in all 4 quadrants of the body for more than 3 months, and pain in a minimum of 11 of the 18 designated tender spots when pressure is applied.<sup>18,19</sup> Although no cure is available, treatment can provide symptom relief and function improvement.<sup>10</sup> The therapeutic goals of medication include the management of pain, fatigue, and reduced function, and improving other FM-associated symptoms.<sup>20</sup> Nonpharmacologic approaches to FM include patient education, exercise, alternative therapies, and self-management.<sup>1</sup>

### Drug Therapy

In January 2009, milnacipran HCl (Savella), a dual serotonin-norepinephrine reuptake inhibitor (SNRI), was approved for the management of FM. It is a welcome addition to the limited arsenal of agents available for FM. The 2 other FDA-approved drugs are the anti-convulsant Lyrica (pregabalin), and the SNRI Cymbalta (duloxetine hydrochloride).

Pregabalin is indicated for the management of FM, pain associated with diabetic peripheral neuropathy (DPN), postherpetic neuralgia, and partial-onset seizures.<sup>21</sup> Duloxetine is indicated for the management of FM, depression, generalized anxiety disorder, and DPN.<sup>22</sup> Milnacipran is currently the only agent approved solely for the management of FM.<sup>23</sup>

Milnacipran is available in 4 tablet strengths.<sup>23</sup> Based on findings from 2 pivotal phase 3 clinical trials, treatment with milnacipran 100 mg/day (50 mg twice daily) or 200 mg/day (100 mg twice daily) showed significant and clinically meaningful concurrent improvements across 3 measures of FM—pain reduction, patient global assessment, and physical function.<sup>9,24</sup> Milnacipran is the first and only product approved to treat the symptoms of FM using a composite responder analysis as the primary end point.<sup>21-24</sup>

### Clinical Pharmacology

Milnacipran is indicated for the management of FM in adults ( $\geq 18$  years old). It is not approved for use in patients younger than age 18. The exact mechanism of milnacipran's central pain inhibitory action is unknown.<sup>23</sup> In preclinical studies, milnacipran has been shown to inhibit neuronal norepinephrine and serotonin reuptake, demonstrating a 3-fold more potent inhibition of norepinephrine uptake in vitro than sero-

tonin, without directly affecting the uptake of dopamine or other neurotransmitters.<sup>23</sup> In vitro studies, milnacipran was distinguished from other dual reuptake inhibitors, including duloxetine and venlafaxine, by its selectivity for norepinephrine over serotonin, whereas duloxetine and venlafaxine are more selective for serotonin reuptake inhibition over norepinephrine.<sup>24</sup>

Because milnacipran shows an affinity for the norepinephrine and serotonin receptors, without binding to dopamine, histamine, or muscarinic receptors, it is not associated with many of the side effects of tricyclic antidepressants.<sup>8,23</sup> Milnacipran is well absorbed, with an absolute bioavailability of approximately 85% to 90%, reaching maximum concentrations within 2 to 4 hours.<sup>23</sup> Absorption is not affected by food. Excreted primarily unchanged in urine (55%), milnacipran has a terminal elimination half-life of 6 to 8 hours. Steady-state levels are reached in 36 to 48 hours. Milnacipran has a low degree of binding to plasma proteins (13%).<sup>23</sup>

### Results from Clinical Trials

At the Outcomes Measures in Rheumatology 8 (OMERACT 8) meeting, 23 clinicians with expertise in FM convened to reach consensus on core symptom domains, evaluate outcome measures in clinical trials, and define research agenda. During the meeting, physicians and patients were asked to rank 40 FM-specific domains in relative importance.<sup>25</sup> The top 4 core criteria rated as "essential," in order of importance, were<sup>25</sup>:

- Pain
- Fatigue
- Patient global status
- Multidimensional function.

OMERACT 8 participants agreed that "the ability to measure clinically meaningful change in multiple dimensions of fibromyalgia utilizing a composite responder index is desirable."<sup>25</sup> This formed the clinical end point framework for the milnacipran clinical studies.

The FDA approval of milnacipran was based on the results of 2 randomized, multicenter, double-blind, placebo-controlled US studies that used a composite responder analysis.<sup>9,24</sup> The 2 primary end points were rates of FM composite responders (3-measure composite) and pain responders (2-measure composite). Three-measure composite responders were defined as patients concurrently experiencing clinically meaningful improvements in 3 domain criteria—pain (30% or more improvement in pain), patient global status (rating of very much improved, a score of 1, or much improved, a score of 2, on the patient global impression of change [PGIC] scale), and physical function, defined as a 6-point or more improvement in the Short-Form 36 physical component summary score. Two-measure composite

**Table 1** Milnacipran Multimeasure Responder Analysis Demonstrating Significant Fibromyalgia Relief

Area of improvement	Measure	Threshold for response	2-Measure composite responders <sup>a</sup>	3-Measure composite responders <sup>b</sup>
Pain relief	VAS pain	≥30% reduction from baseline score	√	√
Global improvement	PGIC	Score of 1 or 2: “very much improved” or “much improved”	√	√
Physical functional improvement	SF-36 PCS	≥6 point improvement		√

<sup>a</sup>2-measure composite responders were required to demonstrate simultaneous pain relief and global improvement versus placebo.  
<sup>b</sup>3-measure composite responders were required to demonstrate simultaneous pain relief, global improvement, and physical function versus placebo.  
PGIC indicates patient global impression of change; SF-36 PCS, Short-Form 36 physical component survey; VAS, visual analog scale.

responders were defined as those who met the pain and the PGIC criteria.<sup>9,24</sup>

Pain data for the milnacipran trials were captured via an electronic patient diary that measured pain from a scale of 0 (no pain) to 100 (worst possible pain).<sup>9,24</sup> Patients reported their current level of pain at specific intervals. Data collections were taken in the morning, at 3 to 5 random prompts throughout the day, and in the evening. In the morning report, patients rated their average level of pain in the previous 24 hours; and at the end of a 7-day period, patients rated their average level of pain for the previous 7 days.<sup>9,24</sup> Milnacipran is the only agent approved for the management of FM that collected pain data with the help of an electronic patient diary, which allows for capturing real-time pain data, as well as 24-hour and 7-day pain recall.

The first study included 86 centers and 1196 patients who were randomized to 15 weeks of treatment with milnacipran 100 mg/day, milnacipran 200 mg/day, or to placebo.<sup>9</sup> The second study included 59 centers and 888 patients randomized to 15 weeks of milnacipran 100 mg/day, milnacipran 200 mg/day, or to placebo.<sup>24</sup> Although the primary end point was 3 months, this trial also included a 27-week end point.<sup>24</sup>

Findings from both studies showed that milnacipran achieved a significant response rate compared with placebo in the 2-measure and 3-measure composite at 3 months (Table 1).<sup>9,24</sup> In both studies, a significant decrease in pain was reported as early as week 1 of treatment with a stable dose of milnacipran in patients who reported themselves globally very much or much improved.<sup>9,23,24</sup>

### Adverse Reactions

Milnacipran was found to be safe and generally well tolerated in clinical trials. The most common adverse event (AE) was nausea (37% vs 20% for placebo).<sup>19,22</sup> Other AEs more common (≥5% and greater than

placebo) with milnacipran include headache, constipation, dizziness, insomnia, hot flushes, hyperhidrosis, vomiting, palpitations, heart rate increase, dry mouth, and hypertension.<sup>23</sup>

Overall, premature treatment discontinuation in clinical trials because of AEs was 23% in patients treated with milnacipran 100 mg/day and 26% with milnacipran 200 mg/day compared with 12% of placebo-treated patients.<sup>23</sup> Milnacipran is not associated with a significant incidence of fatigue or somnolence and does not cause weight gain.<sup>23</sup> Patients treated with milnacipran for up to 3 months in both the 100 mg/day and the 200 mg/day treatment groups experienced a weight loss of approximately 0.8 kg, compared with a mean weight loss of approximately 0.2 kg in placebo-treated patients.<sup>23</sup>

### Contraindications

Like other dual reuptake inhibitors, milnacipran's label includes a black box warning about the risk for increased suicidal ideation or behavior in children, adolescents, and young adults with major depressive disorder and other psychiatric disorders.<sup>1</sup> Milnacipran is not approved for use in pediatric patients.<sup>23</sup>

The development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SNRIs and selective serotonin reuptake inhibitors (SSRIs) alone, including milnacipran, but particularly with concomitant use of serotonergic drugs (including triptans), with drugs that impair metabolism of serotonin, including monoamine oxidase inhibitors (MAOIs), or with antipsychotics or other dopamine antagonists. In its most severe form, serotonin syndrome can resemble NMS. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

Milnacipran is also contraindicated for use within

MAOIs concomitantly, or within 14 days of discontinuing an MAOI. A minimum of 5 days should be allowed between discontinuing milnacipran and starting an MAOI.<sup>23</sup>

The SNRIs, including milnacipran, have been associated with reports of an increase in blood pressure (BP). In the 3-month placebo-controlled FM clinical trials, milnacipran treatment was associated with mean increases of up to 3.1 mm Hg in systolic BP and diastolic BP.

Sustained increases in BP could have adverse consequences. BP should be measured before initiating milnacipran treatment and measured periodically throughout the treatment. Preexisting hypertension and other cardiovascular conditions should be treated before starting therapy with milnacipran. Dose reduction or discontinuation should be considered for patients with a sustained increase in BP while taking milnacipran.<sup>23</sup>

Reports of increases in heart rate have been associated with SNRIs, including milnacipran. In clinical trials, relative to placebo, milnacipran treatment was associated with mean increases in pulse rate of approximately 7 to 8 beats per minute.<sup>23</sup>

Heart rate should be measured before initiating milnacipran treatment and measured periodically throughout treatment. Preexisting tachyarrhythmias and other cardiac conditions should be treated before starting therapy with milnacipran. Dose reduction or discontinuation should be considered for patients who experience a sustained increase in heart rate while taking milnacipran.<sup>23</sup>

Withdrawal symptoms have been observed in clinical trials following discontinuation of milnacipran, as with other SNRIs and SSRIs. Patients should be monitored for these symptoms when discontinuing treatment with milnacipran. Milnacipran should be tapered and not discontinued abruptly after extended use.<sup>23</sup>

SSRIs and SNRIs, including milnacipran, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may contribute to this risk. Patients should be cautioned about the risk of bleeding associated with the concomitant use of milnacipran and NSAIDs or other anticoagulants.<sup>23</sup>

Milnacipran should not be used in patients with uncontrolled narrow-angle glaucoma. An increased risk of mydriasis was associated with milnacipran, as has been reported with other dual reuptake inhibitors of norepinephrine and serotonin. Milnacipran should be used cautiously in patients with controlled narrow-angle glaucoma.<sup>23</sup>

Mild elevations in liver enzymes have been reported with milnacipran, and in rare instances, fulminant hepatitis.<sup>23</sup> Increased rates of genitourinary AEs have been reported in male patients with a history of obstructive uropathies.<sup>23</sup>

Exercise caution in patients with substantial alcohol use or chronic liver disease, patients with mania or a history of seizure disorder, and in those with significant hypertension or cardiac disease.

Consult the prescribing information for additional safety information.<sup>23</sup>

### Drug–Drug Interactions

Milnacipran is unlikely to result in clinically significant pharmacokinetic drug interactions because it undergoes minimal CYP450-related metabolism, is predominantly excreted unchanged in urine, and has a low degree of plasma protein binding.<sup>8,23</sup> However, pharmacodynamic interactions may occur with lithium, epinephrine and norepinephrine, serotonergic drugs, digoxin, clonidine, clomipramine, CNS-active drugs, and MAOIs.

As noted, concomitant use of NSAIDs and other anticoagulants with SSRIs or SNRIs, including milnacipran, may increase the risk of bleeding events.<sup>23</sup>

### Dosing and Administration

Milnacipran is available in 12.5-mg, 25-mg, 50-mg, and 100-mg tablet strength. Except for the first-day dose of 12.5 mg, milnacipran is administered in 2 divided doses/day, with a recommended dose of 100 mg/day (or 50 mg twice daily) after day 7. For initial dosing, milnacipran is titrated according to a specified schedule (Table 2) and is available in 2 titration pack options. The dose may be increased to 200 mg/day (or 100 mg twice/day), based on patient response. Doses above 200 mg/day have not been studied.<sup>23</sup>

Milnacipran can be taken with or without food; however, when taken with food, it may improve tolerability in patients who experience nausea. After extended use, milnacipran should be reduced gradually rather than discontinued abruptly. The maintenance dose should be reduced by 50% in patients whose creatinine clearance is <30 mL/min. No dosage adjustment is indicated for mild renal impairment or for patients with hepatic insufficiency.

Milnacipran is nonnarcotic and is not categorized as a scheduled substance by the US Drug Enforcement Administration.<sup>23</sup>

Milnacipran use in specific population is as follows<sup>23</sup>:

- As a pregnancy category C agent it should only be used in pregnant women if the potential benefit justifies potential risks to the fetus. Because it is not known if milnacipran is excreted in human milk and its safety in infants is not known, nursing while taking this agent is not recommended.
- It is not recommended in pediatric patients; its safety and effectiveness in patients younger than age 17 years have not been established.

**Table 2 Initial Dosing and Titration for Savella**

Timing	Dose titration
Day 1	12.5 mg
Days 2, 3	25 mg/d or 12.5 mg bid
Days 4-7	50 mg/d or 25 mg bid
After day 7	100 mg/d or 50 mg bid
Start-up titration pack options	
2-wk titration pack	Includes 1-wk titration and 1 wk of 100 mg/d dose
4-wk titration pack	Includes 1-wk titration and 3 wks of 100 mg/d dose

*Note:* Although Savella is nonnarcotic, prescription should be written for the smallest quantity of tablets consistent with good patient management to reduce the risk of overdose.

- Because milnacipran is primarily excreted unchanged through the kidneys, with an expected decrease in renal function associated with age, renal function should be considered before prescribing milnacipran in elderly patients. It has been associated with hyponatremia in elderly patients, who are at increased risk for this.
- This medication is not recommended in patients with end-stage renal disease, and should be used with caution in those with moderate renal impairment or severe hepatic impairment.

**Cost**

The cost of Savella is \$3.38/day. In comparison, Lyrica costs \$4.28/day, and Cymbalta \$4.00/day. These costs reflect wholesale acquisition cost per labeled daily dose. Net costs varies by health insurance plan.

**Conclusion**

Patients with FM have many comorbidities and high levels of healthcare utilization and costs. Increased education and awareness about FM, earlier diagnosis, and improved management approaches, including effective new treatments, may lead to improved patient outcomes and subsequent reductions in utilization and costs.

Milnacipran is the most recent addition to the limited number of FDA-approved drugs for the management of FM. Milnacipran is an SNRI that blocks reuptake of norepinephrine with approximately 3 times greater potency in vitro than serotonin.

Milnacipran delivers simultaneous improvements on 3 key aspects of FM, has a low potential for pharmacoki-

netic drug–drug interactions, and is not associated with a significant incidence of fatigue or somnolence, or weight gain. It offers economic value compared with other agents approved for the management of FM. ■

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## Composite Outcomes for Fibromyalgia

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**RESEARCHERS:** Fibromyalgia (FM) is a complicated disease. Until the American College of Rheumatology came up with standardized criteria on its classification, it has been very difficult to study. These common criteria were created from the perspective of care providers to facilitate identifying patients, not from a patient perspective. To evaluate clinical benefit, however, a patient perspective is central, and a composite outcome measure incorporating patient-centered outcomes was used in 2 milnacipran registration trials.

Composite measures are appropriate when it is not clear what end point is most important or if more than 1 is thought to be important, and individual outcomes selected to be a part of the composite are related across a spectrum of benefit. For milnacipran, the composite outcome measure used met this standard and consisted of 3 measures: (1) an improvement in pain from baseline, (2) a global rating scale, and (3) an improvement in physical function.

Composite measures are often used when individual ones are insufficient to determine effects of importance. For example, if events are rare, a composite of several different measures or events can be used to best capture the effects of an intervention.<sup>1</sup> Composites are frequently used in cardiology, where composites of individual components such as cardiovascular mortality, revascularization, and myocardial infarction are lumped together into a single measure.<sup>2</sup>

Several guiding principles are paramount when using and designing good composite measures for efficacy and effectiveness. First, individual components of a composite outcome should be similar in importance when considered from a patient perspective.<sup>1</sup> Interpreting a composite outcome is difficult enough, so that mixing “apples and oranges” in terms of clinical importance only further complicates their use. Often death is included in a composite measure. This practice is widespread, but a patient dying, by definition, disallows any subsequent events of different measures within a composite to occur. In the case of milnacipran, the 3 outcomes chosen are of similar importance, and rather

than arbitrarily selecting only 1 outcome of interest, the composite facilitates use of all 3.

A second principle in using a composite measure is to increase power and ability to examine differences between the intervention and the control groups.<sup>3</sup> If individual events are infrequent, for example, a composite measure composed of several related individual measures may increase statistical efficiency. Although not necessarily the case for FM, the measures chosen can be considered a form of “hedging bets,” so that the trial will be adequately powered.

A final principle relates to the magnitude of each individual measure’s effect size. These should be similar; otherwise 1 measure may drive results in a composite.<sup>4</sup> For example, if the pain improvement criteria were met in 80% of patients, and the functional status criteria in only 20%, the overall composite would be unbalanced and would not truly reflect functional status. For milnacipran, improvements had to occur in at least 2 measures for a given patient, further ensuring that no single component could drive the results.

The composite measure for FM effectiveness represents a good application of the principles of composite design and of criteria selection. In the future, as our understanding of the disease process evolves and new types of drugs are developed, new composite measures will be required. It is hoped that they would live up to the standard set with milnacipran. ■

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## Management of Fibromyalgia

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**PAYERS:** Fibromyalgia is a complex syndrome that is characterized by diffuse pain associated with a host of other symptoms, including fatigue, sleep disturbances, morning stiffness, cognitive dysfunction, headaches, and feelings of anxiety and depression. This syndrome is far more prevalent in women and may affect up to 4% of the US population.

Fibromyalgia often presents with vague complaints and is often incorrectly diagnosed by clinicians. This may lead patients with fibromyalgia to seek care from multiple physicians; these patients often undergo a significant number of diagnostic tests before a correct diagnosis is reached. Data have shown that patients with fibromyalgia, on average, spend more than 3 times as much money and time on healthcare as do matched populations without this condition. A significant amount of spending for these patients is for diagnostic studies and for medications, often targeted at the relief of pain. Despite this cost and the use of healthcare resources, patients with fibromyalgia often suffer a reduced quality of life, and their ability to be productive members of the workforce is affected.

The present article describes a new medication, milnacipran HCl (Savella), a serotonin-norepinephrine reuptake inhibitor (SNRI), which has been shown in clinical trials to improve many of the symptoms associated with fibromyalgia. Most important, this agent demonstrated significant improvement in fibromyalgia composite responders (defined as those with meaningful improvements in 3 clinical domains—pain, patient global assessment, and physical function)—as well as fibromyalgia pain responders (defined as the patient meeting both pain and global change criteria).

Although this agent is not a cure for fibromyalgia, it does add an additional tool for the clinician to use in the treatment of this complex syndrome. Milnacipran joins pregabalin (Lyrica) and duloxetine HCl (Cymbalta) as the only agents FDA-approved for the management of fibromyalgia. In addition to these 3

agents, a broad range of medication classes—anticonvulsants, antidepressants, anti-inflammatory drugs, as well as pain relievers that include opioids—are used “off-label” for the treatment of fibromyalgia.

With the approval of a new SNRI for the management of fibromyalgia, P&T Committees will be asked to review the treatment options for fibromyalgia, which will include a review of the 3 FDA-approved agents and of agents frequently used “off label” for the treatment of fibromyalgia. In the absence of head-to-head data comparing the 3 FDA-approved agents, and with virtually no data to compare these agents to the many drugs that are currently used “off label” for the treatment of fibromyalgia symptoms, it will be a challenge for P&T Committees to assess this category. P&T Committees therefore must consider differences in mechanisms of action, pharmacokinetic profiles, efficacy outcomes, as well as the criteria for determining such outcomes, safety, and tolerability, when making their decisions. It is likely that we shall continue to see significant variability of formulary tier-placement decisions made by different P&T Committees. Similarly, some committees may choose to implement clinical management programs, for this agent, much as we have seen for the other agents in the class.

P&T Committees will continue to be challenged in this category to provide the right balance of patient access, clinical outcomes, and cost management. Having comparative clinical trial data and outcome studies would certainly help facilitate these decisions, but this information is generally not available in the early post-approval phase. Without that information, P&T Committees will need to carefully evaluate new treatment options based on existing data to make appropriate treatment options available for this complex and costly illness. ■

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*Continued*

## Composite End Points and the Impact of Milnacipran on Patients with Fibromyalgia

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**PROVIDERS:** The recent approval of milnacipran hydrochloride (Savella) for the management of fibromyalgia (FM) was based on clinical trials showing that a significantly greater proportion of patients taking milnacipran compared with those taking placebo met the prespecified criteria for being a responder based on a composite end point. Of the drugs approved for the management of FM, only clinical trials of milnacipran incorporated a composite end point to establish efficacy.

Composite end points have been used to evaluate the clinical efficacy of several therapies for the treatment of asthma,<sup>1</sup> migraine,<sup>2</sup> organ transplantation,<sup>3</sup> myocardial infarction,<sup>4</sup> and diabetes,<sup>5</sup> exemplifying a growing trend in the use of this type of end point. Moreover, several expert panels, such as the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) group, have encouraged the use of composite end points in the evaluation of new medicines. What is the relevance of composite end points when trying to understand the impact of milnacipran on patients with FM?

Clinically, composite end points are considered to be more robust and meaningful than analyses of group mean changes on a single, continuous end point such as pain for several reasons. First, assessing milnacipran's composite end points—pain,<sup>6</sup> the patient global impression of change (PGIC),<sup>7</sup> and physical functioning<sup>8</sup>—ensures that the therapy is producing clinically significant improvements in multiple domains simultaneously, in the same patient. In contrast, a continuous analysis of change in pain reflects only group mean differences, which may not necessarily reflect the actual change observed for any given patient. In addition, relying on multiple group-level comparisons across different end points does not ensure that reductions in pain and improvements in functioning, for example, are occurring in the same group of patients.

Second, estimates of efficacy derived from composite end points reflect a conservative, worst-case profile of a drug's efficacy. This is because patients who fail to meet the composite responder threshold may have experienced clinically meaningful changes in 1 or more domains but fail to qualify as a responder because of their response on a single domain.

Third, because PGIC ratings are thought to reflect each patient's global evaluation of the balance of the efficacy of a drug against its tolerability, incorporating PGIC ratings in the composite end point broadens the evaluation beyond efficacy to include tolerability as well.

Fourth, by incorporating a measure of function, the ability of the therapy to not only treat symptoms but also help to return the patient toward more normal functioning is assessed. Therefore, the composite end points used in milnacipran's clinical development program speak to a more comprehensive analysis of its efficacy and tolerability from the individual patient's perspective.

Composite end points also have shortcomings. While composite end points have the potential to increase the statistical power of clinical trials by elevating the observed event rate through aggregating multiple end points, the converse can be true if the various domains are not all equally responsive to therapy.<sup>9</sup> For example, if improvements in physical functioning are harder to achieve than reductions in pain, which is potentially the case for patients with FM, then the percentage of patients reporting improvements in physical functioning sets a ceiling for the maximum percentage of patients who can qualify as composite responders. Composite end points can only be as robust as the end point most difficult to change, and they require that the therapy produces clinically significant changes in multiple domains in the same patient. As such, they can set a high hurdle for success.

The use of composite end points in drug development is likely to increase. In the case of milnacipran, the use of composite end points provides a conservative estimate of the rates of clinically meaningful, multidimensional change in patients with FM. ■

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